# Overview of Long-Term Goal 1: Integrated Risk Information System (IRIS) and Other Priority Health Hazard Assessments

## Background

The mission of the U.S. Environmental Protection Agency (EPA) is to protect public health and the environment. The Clean Air Act, the Safe Drinking Water Act, the Comprehensive Environmental Response, Compensation, and Liability Act (Superfund), the Toxic Substances Control Act, and other environmental laws provide the statutory authority for EPA to carry out its mission. To protect public health, EPA limits human exposure to environmental contaminants by regulating releases of chemicals and other substances to the air, water, and land, and by reducing concentrations of contaminants already in environmental media. The scientific support for decisions about the safety of substances in the environment is provided in risk assessments performed by EPA Program Offices and Regions. The Human Health Risk Assessment (HHRA) Program contributes directly to this effort to protect public health by providing state-of-the-art hazard identification and dose-response assessments that, when combined with site- or problem-specific exposure assessments, provide estimates of risk that can be used to determine acceptable levels of release of contaminants to the environment, safe drinking water and food concentrations, and clean-up levels at waste sites, to name just a few of the applications. The HHRA Program ensures that EPA has high-quality, peer reviewed toxicological information for its assessments and promotes consistency across the many and diverse EPA programs that use risk assessment to support decision making.

Under Long-Term Goal (LTG) 1 of the HHRA Program, EPA's Office of Research and Development (ORD) conducts health assessments of priority environmental contaminants needed by EPA's programs and Regions to carry out their legislative mandates. The main components of LTG 1 are the Integrated Risk Information System (IRIS) and Provisional Peer Reviewed Toxicity Values (PPRTVs). IRIS assessments and PPRTVs provide EPA with hazard identification and toxicity values derived from quantitative dose-response assessment. ORD also conducts complete risk assessments, including exposure assessments, to provide scientific support for decisions in emergencies involving potential risks to public health. The HHRA Program played a significant role in responding to the World Trade Center and Hurricane Katrina emergencies and analyzing environmental risks in the aftermaths.

HHRA assessments are widely used by EPA as well as by States and U.S. and international regulatory agencies because of their high quality, which is maintained through rigorous review and scientific peer consultation. Every assessment receives peer review by scientists in EPA and by outside experts. The review cycle for IRIS assessments includes internal EPA review, interagency review by interested agencies of the Federal government, public review and comment, and a face-to-face external panel. Assessments designated as "highly influential," such as the perchlorate, trichloroethylene, and tetrachloroethylene assessments are often reviewed by special panels of the National Academy of Sciences (NAS). After each round of

review, an assessment is revised to the extent necessary to address comments and a disposition of comments is prepared. The HHRA program is the only Federal program that provides qualitative and quantitative assessments of both cancer and noncancer risks. No other Federal health assessment program has a similar mission, scope, and peer-review process.

The purpose of this LTG description is to portray, in concert with poster presentations, the Program's relevance to EPA decision-making, leadership in risk assessment, scientific quality, and performance. Ongoing assessments are used to illustrate these attributes. Linkages to the methods, models, and guidance developed under HHRA LTG 2 are highlighted.

## Relevance

HHRA's health assessments meet a specific and continuing need by providing a common scientific foundation for decision-making within EPA programs. HHRA toxicity values are combined with problem-specific exposure information to develop risk estimates. These risk estimates are the scientific input EPA decision-makers use in setting standards for the release of chemicals to air, water, and land; determining safe clean-up levels at contaminated sites; and setting allowable levels of chemical residues in food and drinking water, consumer products, and indoor and outdoor environments.

IRIS is EPA's preferred source of health effects information. EPA's Superfund Program, for example, specifies a hierarchy of sources for risk assessment toxicity values in which IRIS assessments and PPRTVs are ranked first and second. IRIS assessments are disseminated to EPA and the public on a web-based Internet site (www.epa.gov/iris). Currently, IRIS assessments for over 540 chemicals are available on the IRIS web site. Users include not only EPA Program Offices and Regions but also other Federal, State, and local agencies (at national and international levels) and the public, including academia, regulated industries, environmental organizations, and individuals. To ensure that the IRIS program conducts the highest priority assessments, nominations are solicited annually from EPA Program Offices and Regions, other Federal agencies, and the public. Criteria for selection include EPA statutory, regulatory, or programmatic need; potential public health impact; availability of science or methods to develop or update an assessment; Federal, State, or other user needs; availability of health assessments from other organizations to leverage resources; and availability of EPA resources to conduct the assessment. PPRTVs are prepared for selected contaminants at the specific request of OSWER's Superfund Program and are reviewed and updated every 3-5 years

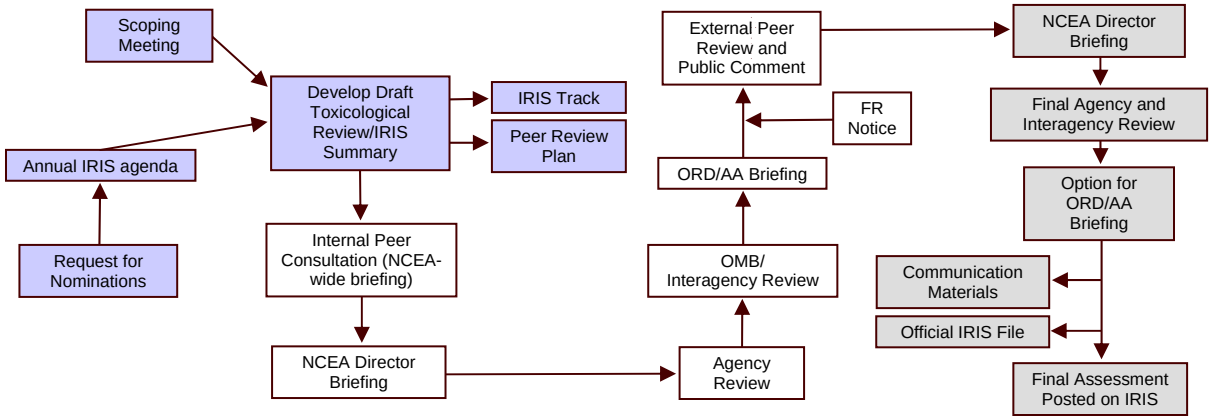
## Quality and Leadership

ORD is the global leader in conducting state-of-the-science health risk assessments. LTG 1 assessments are often the first to apply new EPA risk assessment guidelines and new scientific methods and data. IRIS assessments and PPRTVs rely on peer-reviewed epidemiological and laboratory animal studies to identify hazards associated with exposure to environmental contaminants and to perform quantitative dose-response analysis. Biologically based mathematical models and data on the modes of action (MOAs) by which chemicals exert their

toxic effects are used to answer questions about the human relevance of animal studies, to extrapolate between animals and humans, to identify and assess sensitive subpopulations, and to select appropriate methods to extrapolate from high experimental doses to the low doses people encounter in the environment. Quantitative methods for characterizing uncertainty in toxicity values are being applied. Based on EPA client office needs, the program has expanded its products beyond assessments for chronic exposure conditions to include less-than-lifetime assessments and dose-response assessments for mixtures. As these new methods are applied in assessments developed under LTG 1, methodological gaps have been identified. The LTG 2 methods development program is designed both to fill the gaps in our current methods and to lead the risk assessment field in developing and applying new methods.

In the accompanying posters, we have provided overviews and examples of the methods and processes involved in preparing HHRA assessments.

**Poster 1, Integrated Risk Information System (IRIS),** illustrates the IRIS document development process. The process begins with an annual Federal Register Notice publicizing the current IRIS agenda and new starts, followed by the development of a draft assessment. As illustrated in the figure below, the draft assessment undergoes a multi-layer review, starting with internal peer review, followed by agency-wide review, interagency review across the Federal government, an external peer review and public comment; and finally posting on the IRIS database.




**Poster 2, Provisional Peer Reviewed Toxicity Value Documents (PPRTVs),** describes how, through PPRTVs, the HHRA program provides EPA's Office of Solid Waste and Emergency Response (OSWER) with interim toxicity values on accelerated schedules. Chemicals are selected according to priorities set by the Superfund Program. PPRTVs are OSWER's preferred source of peer-reviewed health assessments when IRIS values are not available to support decision-making for cleanup levels and prioritization of activities at Superfund sites.

**Poster 3, Incidence Response Assessment Activities,** details how ORD-conducted risk assessments contribute to assessing possible human health risks in environmental emergencies. ORD conducts risk assessments that combine health assessments done for IRIS and PPRTVs with exposure data to derive estimates of risk that help EPA determine how to respond. ORD

estimated the risks associated with the aftermath of the attacks on the New York World Trade Centers and the environmental impact of Hurricane Katrina on the Gulf Coast region. ORD is currently assessing the risks associated with asbestos exposure in Libby, MT, a former mining area.

**Poster 4, IRIS Acrylonitrile Assessment – State of the Art Assessment,** uses the ongoing draft IRIS assessment of acrylonitrile as an example of an HHRA state-of-the-art assessment. Human data from occupational epidemiological studies are used to derive a Reference Concentration (RfC) and cancer Inhalation Unit Risk. Animal data are used to derive the Reference Dose (RfD) and oral Cancer Slope Factor. Internal dose metrics are estimated using a physiologically based pharmacokinetic (PBPK) model. MOA analysis is applied to determine application of age-dependent adjustment factors (ADAFs).

**Poster 5, Use of Epidemiologic Data in IRIS Assessments,** describes how human data are used in hazard identification and dose-response assessment. Most often, the available human data are from occupational epidemiological studies. The quantity and quality of epidemiological studies of chemical exposures have grown over the past 20 years, and HHRA assessments increasingly rely on human data in hazard identification, development of toxicity values, determination of MOAs, development and use of biologically based models, and identification of data gaps.

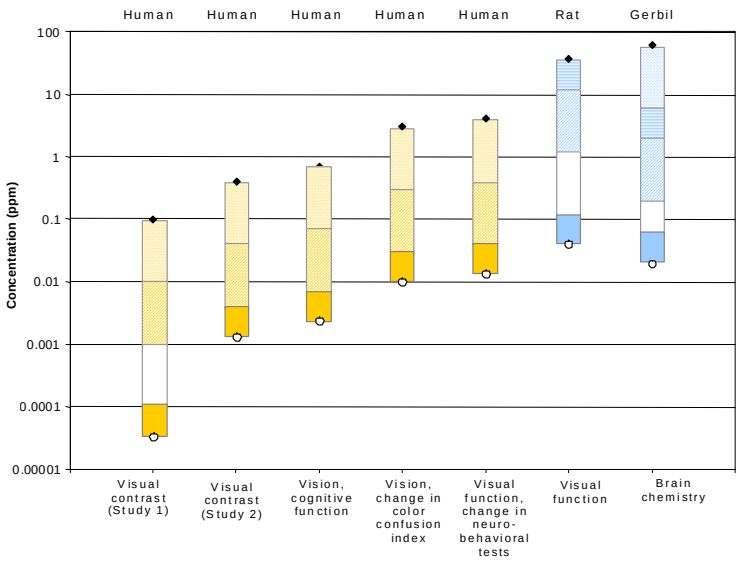
Following the 2005 EPA *Guidelines for Carcinogen Risk Assessment,* HHRA assessments routinely consider the MOA(s) of carcinogens in evaluating relevance of data to human risk estimation and in selecting approaches to extrapolation from high experimental doses to the low doses generally encountered in the environment. **Poster 6, Linear and Nonlinear Approaches for Human Health Risk Assessment,** describes how MOA information informs low-dose.

MOA information can also help to identify susceptible subgroups of the exposed population. The HHRA Program applies the EPA *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens,* which recommends that if a chemical induces tumors via a mutagenic MOA, adjustments should be made to the cancer potency values. **Poster 7, Assessment of Early-Life Exposures and Application of Age-Dependent Adjustment Factors (ADAFs) to Chemical Carcinogens with a Mutagenic Mode of Action,** describes how scientists in the HHRA Program have taken a leading role in implementing this EPA guidance, as illustrated in the draft acrylonitrile and draft ethylene oxide assessments, and have provided technical guidance to the Office of Air and Radiation (OAR) on evaluating the mutagenicity of coke oven emissions for use in rule-making. Under LTG 2, the HHRA Program is developing a better understanding of the implications of MOAs on low-dose extrapolation, on the human relevance of animal tumors, and on human variability, with a focus on genetic polymorphisms and lifestage (see LTG 2, Posters 4, 5, and 6).

A closely related aspect of the increased use of biological data in risk assessment is the application of PBPK models to extrapolate between routes and durations of exposure and between animals and humans. **Poster 8, Physiologically-based Pharmacokinetic (PBPK) Model Applications in IRIS,** describes two examples of PBPK models used in IRIS assessments. A PBPK model is being used in the draft IRIS acrylonitrile assessment to describe the dosimetry of the parent compound and its metabolite, 2-cyanotheylene oxide, in blood to

derive the RfD, the oral Cancer Slope Factor, and the cancer Inhalation Unit Risk. A PBPK model was used in the IRIS assessment of 1,1,1-trichloroethane to derive a chronic RfC and a less-than-lifetime RfC and to extrapolate between routes of exposure. A parallel activity under LTG 2 addresses methods for development, evaluation, and use of PBPK models in risk assessment (see LTG 2 posters 2 and 3). The methods development program is extending biological modeling beyond kinetics to the modeling of a chemical's interactions at the cellular and molecular target levels in dynamic biological processes (toxicodynamics) (see LTG 2 Posters 6-7).

**Poster 9, Benchmark Dose Modeling and Its Application in EPA Chemical Assessments** describes application of advances in quantitative dose-response modeling**.** Benchmark dose modeling (BMD) is now the preferred approach to determining a POD for applying uncertainty factors to develop reference values and for cancer low-dose extrapolation. BMD modeling has advantages over the use of a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-effect level (LOAEL) as a POD in that it uses more of the data available from studies, is less dependent upon the doses used in the study, and accounts for poor study design by generally producing a lower POD for studies of poor quality. Examples of BMD methods in evaluating dichotomous (1,2-dibromoethane), continuous (toluene), and nested dichotomous (methyl ethyl ketone) data are provided. Under LTG 2, ORD has developed Benchmark Dose Software (BMDS) and works to update and expand BMDS capabilities and to train EPA risk assessors in its use (see LTG 2 Poster 8).




How uncertainties in health assessments are analyzed and described is discussed in **Poster 10, Characterizing Uncertainty in IRIS Assessments.** The HHRA Program has increased its emphasis on the presentation of scientific uncertainties in assessments. One approach is to array PODs and toxicity values that might be estimated from all adequate studies in the data base as shown in the chart. Examination of scientific uncertainties can ensure understanding of all the steps, logic, key assumptions, limitations, and decisions in the assessments. LTG 2 Poster 11 describes the HHRA Program's work to identify sources of uncertainty and develop methods for quantifying uncertainty in cancer and noncancer assessments.

**Poster 11, Concentration x Time Relationships,** describes application of methods to estimate toxicity values at various exposure durations. Because health assessments for chronic exposure do not meet all of the needs of EPA risk assessment, assessments have been expanded beyond chronic, individual chemical assessment to less-than-lifetime durations. OAR, the Superfund

Program, and the Homeland Security Program, to name three, often need reference values for short exposure durations, ranging from 30 minutes to 24 hours. The HHRA Program is developing methods for assessing these short exposures and has applied them in assessments for acrolein, ethylene oxide, hydrogen sulfide, hexachlorocyclopentadiene, and phosgene.

**Poster 12, HHRA Program Assessment Products: Outreach, Use, and Impact,** describes the HHRA Program's outreach activities and the use and impact of its products. The HHRA Program collaborates with other Federal programs and with related State and private programs to insure that all critical information is considered during the development of an assessment. One example of HHRA's collaboration with other Federal programs is the interagency review of HHRA products coordinated by U.S. Office of Management and Budget. In addition, interagency working groups have been established to coordinate inputs to major health assessments, including those for dioxin, trichloroethylene, and perchlorate. The HHRA Program coordinates with the Agency for Toxic Substances and Disease Registry (ATSDR) under a Memorandum of Understanding, which calls for the two programs to share the results of literature searches and analyses of chemicals of interest to both. ORD has sought consultation with the National Academy of Sciences (NAS) on recurring and significant risk assessment issues. Through an EPA-funded contract mechanism, NAS convenes expert panels in public workshops to discuss mutually agreed upon risk assessment issues. In 2007, workshops have been held addressing uncertainty in human cancer risk assessment based on bioassay results and implications of receptor-mediated events. A workshop on the use of mouse liver tumors in risk assessments will be held in November 2007. An analysis of the use of HHRA products at Superfund sites shows that 84% of the chemicals assessed at a sample of 10 Superfund sites were addressed in IRIS or PPRTV assessments. For the 135 chemicals assessed in the National Air Toxics Assessment, 69% relied on IRIS assessments for toxicity information. The HHRA Program has set ambitious targets to expand and update its coverage of chemicals of concern to EPA. Achieving these ambitious targets will require addressing significant scientific issues in complex health assessments that interpret and applying state-of-the-science information.

## Program Performance

Key accomplishments in 2005 through 2007 are listed in Table 1.

To chart progress, LTG 1 of the HHRA Program has a long-term performance measure that focuses on outcomes and reflects the program purpose of providing peer-reviewed health assessments of priority environmental contaminants.

The HHRA Program measures the percentage of EPA regulatory decisions that use its peer-reviewed products. The four EPA Program Offices (OAR, Office of Water, OSWER, and OPPTS) and the EPA Regional Offices use the assessments developed by the HHRA Program as scientific support for their regulatory programs. The LTG 1 performance measure is based on use data obtained for selected EPA programs where such data are readily available. These include the National Drinking Water Criteria (DWC) from the Office of Water, the National Air Toxics Assessment (NATA) and Residual Risk Assessments from the OAR, and Superfund Records of Decision. Excluding chemicals with IRIS assessments more than 10 years old that

have new studies that could possibly change a toxicity value, the total coverage by the IRIS data base ranges from 30 to 50% for these programs. These percentages reflect the fact that many needed toxicity values are not available from any source because the data are unavailable to support a quantitative assessment. Thus, for example, while IRIS and PPRTV assessments are available for over 80% of chemicals assessed at some Superfund sites, the actual percentage of needed toxicity values at the sites may be closer to 40-50% because of lack of data available to develop some of the values (LTG 1 poster 12).

***Table 1.***
***Key Accomplishments in 2005-2007***

- **IRIS assessment milestones**
  - **36 draft assessments completed for agency review**
  - **36 draft assessments completed for interagency review**
  - **12 draft assessments posted for public comment and external peer review**
  - **8 assessments posted on database**
  - **NAS review of key issues in trichloroethylene assessment**
- **PPRTV assessments**
  - **PPRTVs for more than 100 chemicals provided to OSWER**
- **Application of 2005 cancer guidelines**
  - **2005 EPA *Guidelines for Carcinogen Risk Assessment* applied in all LTG 1 assessments**
  - **Age-dependent adjustment factors from the *EPA Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* incorporated into IRIS assessments. Ethylene oxide assessment in external peer review.**

## Conclusions

LTG 1 of the HHRA Program is a vital contributor to EPA's risk assessment efforts. ORD will continue to work to improve the performance, coverage, and quality of the program. We plan to post 16 final assessments per year on the IRIS database starting in 2010, update all IRIS assessments over 10 years old that have new studies which might support a revised toxicity value, and complete 50 new or updated PPRTVs for the Superfund Office per year. The PPRTV goal requires us to update about 200 assessments over the next 2 years. In order to achieve these goals, the program will

- increase production of IRIS assessments and PPRTVs,
- accelerate the updating of IRIS assessments that are more than 10 years old and have been identified as having new data that could change a toxicity value or cancer descriptor,
- incorporate new state-of-the-science methods as they become available, and
- maintain high quality through rigorous peer review.